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The periaqueductal gray (PAG) has been shown to be a critical center in mediating endogenous pain modulation. Though the mechanism by which PAG mediates descending pain modulation has been well studied, it is not clear how sensory information coming from different brain regions is incorporated into the PAG and communicates with the downstream brainstem targets. To understand the input/output (I/O) anatomical organization of PAG information processing, we used viral-genetic tracing tools to visualize and quantitatively characterize connections to the PAG.

To determine the inputs coming into the PAG we injected retrograde transsynaptic virus canine adenovirus 2 Cre (Cav2 Cre) into the PAG in Ai32 transgenic mice (express ChR2-EYFP in a Cre-dependent manner). In our preliminary studies using this approach, we observed the robust ChR2-EYFP labelling in several brain regions and spinal cord suggesting these regions make monosynaptic input to the PAG. In our future studies we will be able to stimulate these input regions using blue light and determine the functional role of these inputs to the PAG. To determine the functional role of the PAG outputs to RVM, we used an intersectional genetic strategy that allowed us to specifically target PAG→RVM neurons and manipulate their activity using ChR2. In Vglut (glutamatergic) and Vgat (GABAergic) Cre mice, we injected CAV-FLEx^{loxP}-Flp virus in the RVM and we injected Cre and Flp dependent ChR2-EYFP into the PAG.

This approach allows us to express ChR2 selectively in the Vglut2^{+} or Vgat^{+} PAG→RVM neurons and manipulate their activity to dissect their role in pain processing. In our preliminary studies, we were able to genetically isolate the Vglut2^{+} PAGàRVM neurons.

Optogenetic stimulation of ChR2 expressing Vglut2^{+} PAG→RVM neurons resulted in robust analgesia in a $_{persistent}$ pain model. These results reveal the essential role for I/O organization of the PAG in processing pain information.